Oral and Non-Oral Combination Therapy for Erectile Dysfunction

Ajay Nehra, MD, FACS

Department of Urology, Mayo Clinic College of Medicine, Rochester, MN

An estimated 30 million men in the United States suffer from varying degrees of erectile dysfunction. Increasing age and comorbidities are likely to increase the number of men who are initially refractory or become refractory to phosphodiesterase (PDE)-5 inhibitors, the most popular oral therapy. Combination therapy, a concept well proved in other areas of medicine, is therefore of increasing importance. Combination oral and non-oral (intracavernosal injection and intraurethral application) therapies have been shown to salvage monotherapy. The early introduction of combination therapy has been shown to expedite both the return of natural function and PDE-5 inhibitor responsiveness in post-prostatectomy patients with no reports of serious adverse events. Larger controlled studies are needed to corroborate those encouraging findings.

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Since the US Food and Drug Administration (FDA) approval of sildenafil in March of 1998 over 20 million men in the United States have been treated for erectile dysfunction (ED), defined as the consistent inability to achieve and/or maintain an erection satisfactory for sexual function. The total of men with varying degrees of ED in the United States is estimated to be as high as 30 million. According to the Massachusetts Male Aging Study, 52% of men over 40 experience ED,[1] with an estimated increase of 33% due to the aging of the population and other factors such as increases in weight, dietary changes, smoking behavior, and an emerging increase in diabetes by 2020.[2,3] As the population ages

and the number of comorbidities increase, the degree of ED severity will increase in the aging population.[1]

The link between vascular and erectile dysfunction was described in 1940 by Rene Leriche as a syndrome characterized by the triad of symptoms consisting of absent or diminished femoral pulses, claudication or pain with walking in the buttocks and legs, and "penile impotence."[4] ED for years was thought to be associated with obstructed penile vessels. As our understanding of the pathophysiology of ED has increased, we recognize the importance of the endothelium and the role of endothelial disease in the pathophysiology of peripheral vascular disease. The close link between endothelial dysfunction and ED is increasingly recognized and accepted. ED has been suggested as an early sentinel marker for cardiovascular disease.[5-7] In one study in men with coronary artery disease, ED preceded the coronary symptoms by as many as 3 years.[8,9] Making the diagnosis of ED is not only about improving the quality of life but also potentially important in improving longevity. The medical therapy of ED includes several classes of drugs with different mechanisms of action. This review will confine itself to FDA-approved medications for ED.

Oral Therapy: Phosphodiesterase Inhibitors

Phosphodiesterase (PDE)-5 inhibitors (sildenafil, vardenafil, and tadalafil) are the most popular form of ED treatment due to their ease of use. Their mechanism of action is through the competitive inhibition of PDE-5 and requires endogenous nitric oxide (NO) production. The gaseous molecule NO is derived from the neurons and the penile vascular endothelium. With central nervous system stimulation, NO is produced in the penile nonadrenergic noncholinergic neurons and by neuronal nitric oxide synthase (NOS). After the NO diffuses across the neuromuscular barrier, a cascade of events occurs within the smooth muscle cells of the arterioles that results in intracellular calcium sequestration, relaxation of the vascular smooth muscle, and an increase in penile blood flow. Following an increase in penile blood flow, a secondary, flow-mediated release of NO, produced by endothelial NOS, occurs from the vascular spaces of the penile cavernosal tissue, similarly relaxing the smooth muscles within the corpora. The increased compliance allows the penis to become engorged and tumescent, passively occluding the efferent venules and eventually resulting in penile turgidity.

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important second messengers after NO in the creation of the erection but are constantly being destroyed by a family of enzymes called phosphodiesterases. There are 11 such PDEs throughout the body, all with different affinities for cAMP and cGMP. PDE-5 inhibitors have a very high affinity for cGMP. Simplistically, the rigidity of the erection is dependent on the balance between the production and destruction of cAMP and cGMP. With a lack or severe deficiency of the first messenger NO (severe endothelial disease or post prostatectomy nerve damage) there will never be enough cyclic nucleotides to create an erection. Sildenafil has a 10-fold higher affinity for PDE-5 than cGMP, effectively blocking the destruction of the second messenger and allowing men with disease states that negatively impact neuronal and endothelial NOS (hypertension, diabetes, obesity, dyslipidemia, post pelvic surgery) to regain some or all of their premorbid erectile function.

After orgasm or cessation of stimulation, a drop in the NO production causes a decrease in cAMP and cGMP with resulting detumescence. Despite the lack of production of NO, the PDE-5 inhibitor remains in the cell continuously blocking the enzymatic site of PDE until intracellular levels of the PDE-5 inhibitor favor disassociation. The continued intracellular presence of the inhibitor accounts for the empiric observation of the prolonged efficacy of PDE-5 inhibitors well beyond 1 half life.

The overall efficacy of PDE-5 inhibitors, as measured by the global criteria of improved erections, ranges from 40% to 95% depending on the underlying pathologic etiologies for the ED. Men with less severe erectile dysfunction fare much better than men with severe ED. Hence, men with psychogenic erectile dysfunction report satisfaction rates of 90%, whereas men who have had radical pelvic surgery or have diabetes experience satisfaction rates less than 45%.[10] When more strict criteria are used, such as maintainable erections hard enough for successful vaginal intercourse and completion to orgasm or normalization of erectile function by International Index of Erectile Function (IIEF) scores, PDE-5 inhibitor success rates drop significantly.[11] With failure rates as high as 60% in some conditions,[10] it is not surprising that the prescription refill rates are little more than 50%.[12] One must be careful, however, not to overinterpret the low refill rate, as other confounding variables come into play such as relationship issues, adverse events, failure to take medication as prescribed, and unrealistic patient expectations. In addition, tachyphylaxis has not been clinically demonstrated with the PDE-5 inhibitor, but underlying disease processes progress, resulting in men who are PDE-5 inhibitor refractory. The number of initial PDE-5 inhibitor failures and resistant or refractory patients suggests a need, if not a demand, for possible

combination therapies with other agents, a concept seen in virtually all branches of medicine.

Non-Oral Therapy: Alprostadil

The introduction of intracorporal administration of vasoactive material was a major breakthrough in the treatment of ED. Men who were reluctant to undergo a surgical procedure now had an alternative, although to many, penile injections were no less onerous. Introduced as monotherapy by Virag in 1982,[13] injection therapy evolved into combination therapy with as many as 4 different compounds in the injectate as it became clear that combination therapy was more clinically effective than monotherapy.[14,15] Due to patent and regulatory issues, alprostadil was the only agent for which FDA approval was sought. It was approved in 1994.

Intraurethral alprostadil was approved in 1997 as the first non-parenteral treatment for ED. A non-invasive treatment was now available for ED. Though its effectiveness was not as great as parenteral therapy, with efficacy ranging from 30% to 66%,[16-18] it provided a good alternative to penile injection therapy.

The mechanism of action of alprostadil is targeted at the end organ. Alprostadil acts directly on the penile and vascular smooth muscle cells to stimulate the production of cAMP with resulting intracellular calcium sequestration and subsequent smooth muscle relaxation, penile tumescence, and eventual erection. It does not depend on NO or an intact nervous system. Men with pure neurogenic ED respond to significantly lower doses of alprostadil, whereas older men with multiple medical comorbidities do not respond as well.[19,20]

Combination Therapy

As in other areas of medicine where multiple drugs with different mechanisms of action are combined to more effectively treat a condition, it was not long before combinations of oral and non-oral therapies were considered for ED.

The basic scientific foundation for combination therapy has long been established. By taking advantage of the different mechanisms of action either to increase corporal smooth muscle relaxation or decrease its contraction, the combination of different injectable agents was found to be synergistic in producing an erectile response. Bivalacqua and colleagues[21] showed that the erectile response in the anesthetized cat was best when an adenyl cylase agonist (alprostadil), a non-specific alpha adrenergic receptor antagonist (phentolamine), and a non-specific PDE inhibitor (papaverine) were used. The response was superior to single agents of similar or other classes. Intracavernosal pressure, penile length, and duration of erection were significantly improved over single agents. When the same authors injected a PDE-4 inhibitor (cAMP specific) with alprostadil, synergy in erectile quality was observed.[22] In addition, intracellular levels of cAMP as well as cGMP were increased, suggesting mechanistic "cross talk" between the cAMP and cGMP pathways. In vitro experiments have shown that high concentrations of cAMP inhibit PDE-5, and conversely high concentrations of cGMP inhibit PDE-3.[23]

Oral Failures

The men most likely to fail oral therapy are those with peripheral nerve injury after radical prostatectomy or severe vascular disease and long-standing diabetes with subsequent myopathy, vasculopathy, and neuropathy. In a study of 267 men with mixed etiologies for ED, Jarow and associates[24] found an overall satisfaction with PDE-5 inhibitors of 65%. Men with severe erectile dysfunction had a 41% satisfaction rate. Etiology of ED had a significant impact on satisfaction rate, with neurogenic causes of erectile dysfunction (diabetes and prostate surgery) having significantly lower rates than psychogenic or vasculogenic ED.[19] In a randomized, placebo-controlled study of previously potent men between 1 and 4 years from bilateral nerve-sparing surgery, only 27% of men normalized their erectile function on tadalafil therapy, although 62% described improved erections.[25] Brock and colleagues[26] reported vardenafil assisted intercourse success rates among men with severe ED (IIEF $<$ 11) at least 6 months after bilateral neurovascular bundle sparing prostatectomy of 28% versus 4% with placebo. Costabile and coworkers[27] reported the results of intraurethral alprostadil (MUSE®, Vivus; Mountain View, CA) in 384 men at least 3 months from prostatectomy, both nerve-sparing and non-nerve-sparing, enrolled in the placebo-controlled intraurethral alprostadil pivotal trials. Seventy percent were able to have erections sufficient for penetration in the office and 57% were able to have sexual intercourse at home, for an overall success rate of 40%. The post-prostatectomy cohort would be an obvious subpopulation that would benefit from combination therapy.

PDE-5 Inhibitor and Intraurethral Prostaglandin

Intraurethral alprostadil and PDE-5 inhibitors may be combined to treat oral monotherapy failures. This combination maintains the minimally invasive nature of therapy because the prostaglandin does not need to be injected.

In a retrospective study of 63 patients, Mydlo and colleagues[28] reported on the efficacy of combination therapy in men who had failed monotherapy of both sildenafil and intraurethral alprostadil with 18 months

of follow-up. Combination therapy where 50% of patients were post prostatectomy consisted of 100 mg of sildenafil 1 hour before intercourse followed by 1000 μg of intraurethral alprostadil 10-15 minutes before intercourse. IIEF scores improved 114% over baseline (10.8) with combination therapy versus 41% and 77% improvements on intraurethral alprostadil and sildenafil monotherapy, respectively. Intercourse satisfaction and overall satisfaction scores on the IIEF domains showed comparable improvements of 125% and 128% over baseline. No serious adverse events were reported. The most common adverse events in decreasing order were urethral burning (30%), throbbing (20%), headache (17%), nausea (12%), increased glans sensation (14%), dizziness (9%), dyspepsia (11%), and blue vision (6%). All symptoms were described as mild, and no patient discontinued treatment due to adverse events, with no priapism reported. Socioeconomic status, education, and cost were theorized as factors impacting long-term results.

Raina and associates[29] evaluated the sildenafil-intraurethral alprostadil combination in 23 men at least 6 months post radical prostatectomy who were unsatisfied with sildenafil monotherapy of 100 mg. One hour after 100 mg of sildenafil, the men were instructed to insert 500 μg of intraurethral alprostadil. If no response was obtained, the dose was increased to 1000 μg. Nineteen of these 23 men (83%) reported improvement in rigidity and sexual satisfaction. The rate of rigidity score and successful vaginal penetration increased from 38% and 50% to 75% and 70%, respectively. Spousal satisfaction improved from 52% to 69%. Urethral burning was the most common side effect and was transient. No serious side effects occurred, and none of the men discontinued treatment due to side effects.

Nehra and colleagues[30] evaluated 28 patients, 17 post radical prostatectomy (less than 5 months from surgery) and 11 with organic erectile dysfunction, who had failed either sildenafil or intraurethral alprostadil 1000 μg monotherapy. All patients reported an improvement in their erections and were able to perform vaginal penetration with a mean of 3.6 intercourse episodes per month. All were continuing combination therapy at 30 months, with some able to reduce their dose of sildenafil from 100 to 50 mg. None had crossed over to injection therapy or penile prosthesis. No patients experienced postural hypotension, priapism, abnormal electrocardiograms, angina, or peripheral vascular complications.

PDE-5 Inhibitor and Intracavernosal Prostaglandin

Sildenafil may also be combined with intracavernosal prostaglandins (PGEs), although most of the reports evaluate the addition of sildenafil to injection-therapy failures.

McMahon and associates[31] reported their results in 93 men with mixed etiology ED who had failed high-dose injection therapy. Thirty-four percent responded to sildenafil alone, 31% responded to combination therapy, and 35% did not respond at all and went on to penile prosthesis or vacuum device or were lost to follow-up. None challenged with intraurethral alprostadil had success. In men on combination therapy, 4 discontinued due to adverse events (severe headache, facial and truncal flushing, penile pain, dyspepsia, and dizziness). There were no episodes of priapism.[25]

Mydlo and colleagues[32] evaluated the combined use of intracavernosal PGE-1 and oral PDE-5 inhibitors in 34 post nerve-sparing radical prostatectomy patients who had suboptimal response to oral therapy. Eighteen of these men had received 100 mg of sildenafil, and 16 had received 20 mg of vardenafil. These men were subsequently started on 15 or 20 μg of intracavernosal PGE-1. This study did not report the results of combination therapy but did report the effect of injection therapy on the subsequent development of natural and PDE-5 responsive erectile function. Twenty-two of 32 men who continued therapy reported a significant improvement in erections, and some progressed to minimize the use of intracavernosal injections (ICIs) with sustained response. Thirty-six percent were able to discontinue injections because of the return of "good erections."

Nandipati and coworkers[33] combined intracavernosal alprostadil and nightly sildenafil in 22 men immediately after nerve-sparing radical prostatectomy. They were instructed to use the injections 2-3 times per week, but the sildenafil was not required to be timed to the injections. The men used injection therapy until natural sexual function returned. At an average follow-up of 6 months, 50% had return of spontaneous partial erections and 96% were sexually active. Of the larger group, 43% used combination therapy and 57% used injections alone. The study was designed to evaluate the role of combination therapy of alprostadil injection and sildenafil on the early return of function. Both of the previous studies suggest a role for combination therapy in penile rehabilitation after prostatectomy.

Gutierrez and associates[34] added intracavernosal PGE-1 injections in a strictly programmed dosage to 40 men with mixed etiology ED who were unsatisfied with their oral sildenafil therapy. The patients received 4 biweekly 20 μg intracavernous PGE-1 injections along with either placebo or 50 mg of sildenafil capsules. Four weeks after initiation of therapy, the 2 groups were crossed over in terms of

oral therapy. The authors found a significantly higher satisfaction rate among the group receiving PGE-1 and sildenafil combination compared with those receiving either sildenafil alone or PGE-1 and placebo. Table 1 summarizes the results of several combination therapy studies.

Intracavernosal or Intraurethral Alprostadil

In a randomized prospective study of 60 men, 90% of those on ICI of alprostadil achieved erections satisfactory for penetration compared with 60% of those on intraurethral application (IUA) of alpostradil. Similarly after 3 months, intercourse was reported in 87% versus 53% of administrations. On the other hand, pain was reported by 47% of ICI patients versus 7% of IUA patients, resulting in 30% versus 0% of men discontinuing treatment due to pain, in favor of intraurethral alprostadil. Overall withdrawal was 67% for ICI and 17% for IUA. Perception of ease of use was 40% versus 90%, again favoring IUA. No episodes of syncope or priapism were reported.[35]

A major impediment to injection therapy is the concept of penile injections. Despite its theoretical superior efficacy, many men may not submit to injecting themselves. On the other hand all men after radical prostatectomy have already experienced an intraurethral catheter, and many may be more amenable to consideration of intraurethral therapy.

Financially, the costs of injection therapy and intraurethral therapy are virtually identical and approximately twice that of oral therapy. Third-party payers are unlikely to reimburse for combination therapy despite its demonstrated efficacy and safety. The approximate cost of combination therapy may be as much as US $40 depending on the drugs used and third-party coverage.[36]

Safety

The use of the PDE-5 inhibitors in combination with vasoactive compounds is not recommended in their respective package inserts. As such, it should only be entertained in men with advanced ED that is refractory to oral, intraurethral, or intracavernous therapy. Studies on combination therapy have been done accordingly in men with difficult-to-treat ED. The safety of the combination of sildenafil with intraurethral alprostadil has been demonstrated in several series with a combined total of at least 147 men. The patients were predominantly post prostatectomy or demonstrated vascular disease.[28,30,32,37] All patients received their first combination in the office with 100 mg of sildenafil followed 1 hour later by 500 or 1000 μg of alprostadil. Most patients had already experienced both drugs individually without adverse events. No patients experienced priapism or syncope in any studies, despite a reported priapism incidence of 1% in ICI trials[38] and syncopal incidence of 3% in IUA trials.[39] No priapism was reported in the initial IUA trials.[39] Caution is advised and intraoffice combination dosing is recommended as the safety of this combination therapy is not supported by the FDA package insert for any of the drugs.

Summary

With a growing population of men who are initially refractory or become refractory to PDE-5 inhibitors, combination oral and non-oral therapy is of increasing importance. Combination oral and non-oral therapy has been shown to salvage PDE-5 inhibitor, IUA, and ICI failures. The early introduction of ICI or IUA[40] has been

Table 1
Combination Therapy PDE-5 Inhibitor and Alprostadil

				Satisfaction Scores		
Author	N	Etiology	Outcome	Sildenafil	Sildenafil + Intraurethral Alprostadil	Sildenafil + Intracavernosal Injection
Mydlo et al[28]	67	Mixed	IIEF-6	19.8	24.1	–
Raina et al[29]	23	NSRRP	IIEF-5	13.2	18.6	–
Nehra et al[30]	28	Mixed	GAQ (%)	0	100	–
McMahon et al[31]	29	Mixed	IIEF (3+4)	4	–	8.1

PDE, phosphodiesterase; NSRRP, Nerve-Sparing Retropubic Radical Prostatectomy; IIEF, International Index of Erectile Function. IIEF-6, 6 question questionnaire; IIEF-5, 5 question version; IIEF (3+4), sums of question 3 and 4 of the IIEF questionnaire and is common to both IIEF-5 and 6; GAQ, Global Assessment Question.

shown to expedite the return of natural function and expedite PDE-5 inhibitor responsiveness in post-prostatectomy patients. In the published series on combination therapy there have been no cases of priapism, clinical hypotensive episodes, or any serious adverse events, though the total numbers are admittedly small. Larger controlled studies are needed to corroborate those encouraging findings. Men who require combination therapy are frustrated and sometimes desperate. Many do not want to go on to penile prostheses, and the vacuum device is not an acceptable option; yet the cost of long-term combination therapy is prohibitively expensive for many. It is hoped that as the efficacy and safety for combination therapy is demonstrated in larger studies, third-party payers will recognize its utility and provide insurance coverage for this much needed therapeutic regimen. ■

Dr. Nehra is a consultant to VIVUS, Inc.

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Main Points

- An estimated 30 million men in the United States suffer from varying degrees of erectile dysfunction. Those most likely to fail oral therapy have peripheral nerve injury after radical prostatectomy or severe vascular disease and long-standing diabetes.
- Rigidity of erection depends on the balance between the production and destruction of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which are constantly being destroyed by phosphodiesterase (PDE) enzymes. PDE-5 inhibitors block this destruction, whereas alprostadil acts directly on the penile and vascular smooth muscle cells to stimulate production of cAMP.
- Studies have combined intraurethral alprostadil and PDE-5 inhibitors to treat oral monotherapy failures with good results. PDE-5 inhibitors have also been combined with intracavernosal prostaglandins, most often for injection therapy failures, with good results.
- In the published series on combination therapy there have been no cases of priapism, clinical hypotensive episodes, or any serious adverse events, though the total numbers are admittedly small.
- The costs of injection therapy and intraurethral therapy are virtually identical and approximately twice that of oral therapy. Third party payers are unlikely to reimburse for combination therapy.
- Use of the PDE-5 inhibitors in combination with vasoactive compounds should only be entertained in men with advanced ED that is refractory to oral, intraurethral, or intracavernous therapy.

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